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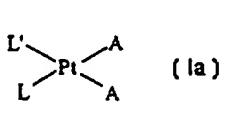
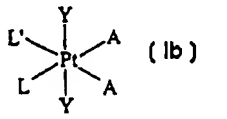
(54) Title: PROCESS FOR PREPARING AMINE PLATINUM COMPLEXES



(Ia)



(Ib)

(57) Abstract

The present invention relates to the area of platinum drugs. In particular, it relates to an improved process for preparing platinum complexes having general formula (Ia) or (Ib), comprising: 1a) a first step, wherein $[PtA_4]^{2-}$ is reacted with L under appropriate conditions in a first solvent to form $[PtA_3(L)]^-$; 1b) a second step, wherein $[PtA_3(L)]^-$ is reacted with L' under appropriate conditions in a second solvent to form cis–$[(PtA_2(L')(L)]$; 1c) in the case there Y is halogen or hydroxy a thrid step, wherein cis–$[PtA^2(L')(L)]$ is reacted with H_2O_2, Y_2 or halogen containing oxidant to form c,t,c–$[PtA_2Y_2(L')(L)]$; in the case where Y is carboxylate, carbamate or carbonate ester a fourth step, wherein an intermediate, where Y is hydroxy formed in step 1c), is functionalized with an appropriate acylating agent; and 1d) in the case where A is not a halide or is different from the original halide, additional step(s) in which the original halide A of an intermediate formed in step 1a or 1b, 1c or 1d is converted to a different halide or a new leaving group(s) A such as mono–dentate hydroxy, alkoxy, carboxylate or bi–dentate carboxylate, phosphonocarboxylate, diphosphonate, or sulphate; wherein L L' and Y have the meaning as defined in the description.

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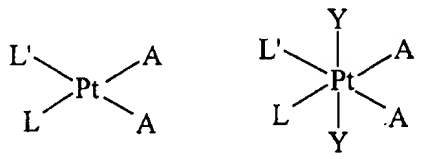
PROCESS FOR PREPARING AMINE PLATINUM COMPLEXES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims benefit of priority to provisional patent application U.S. Serial No. 60/128,939, filed on April 13, 1999, and which is incorporated in its entirety by reference herein.

TECHNICAL FIELD

The present invention relates to the area of platinum drugs. In particular, it relates to an improved process for preparing platinum complexes having the general formula (Ia) or (Ib):



Ia Ib

wherein:

L and L' may be the same or different, provided that L' may be NH_3 , but L may not be NH_3; and

L and L' are each an amine or substituted amine that coordinates to the Pt atom through a nitrogen atom and is a heterocyclic amine or heteroaromatic amine or is represented by NRR'R", wherein R, R', or R" are independently selected from the group consisting of: hydrogen, substituted or unsubstituted straight, branched or cyclic aliphatic, aryl, nonaromatic or aromatic heterocyclic groups; and preferably L is a substituted amine wherein the substituent sterically hinders access of the Pt atom to a DNA strand of cell, preferably a tumor cell; and

A may be the same or different and is a halogen or a leaving group such as hydroxy, alkoxide, carboxylate and may be the same or different or form a bi-dentate carboxylate, phosphoncarboxylate, diphosphonate or sulfate; and

Y is a halogen, hydroxy, carboxylate, carbamate or carbonate ester.

BACKGROUND ART

US Patent No. 4,329,299 and 5,665,771 describe platinum compounds and their usefulness as antitumor drugs. These two patents disclose platinum compounds that encompass complexes of the formula *cis*-[$PtA_2(L')(L)$] and *c,t,c*-[$PtA_2Y_2(L')(L)$], where A is a leaving group such as halogen, hydroxyl or carboxylate, L is an amine coordinated through the nitrogen atom and L' is an ammonium or substituted amine. The process for preparing these complexes disclosed in the patents are known in the art (Hydes, P. C. *US Patent 4,329,299* (**1982**); Murrer, B. A. *US Patent 5,665,771* (**1997**); Braddock, P. D.; Connors, T. A.; Jones, M.; Khokhar, A. R.; Melzack, D. H. ; Tobe, M. L. *Chem.-Biol. Interactions* **1975**, *11*, 145-161; and Giandomenico, C. M.; Abrams, M. J.; Murrer, B. A.; Vollano, J. F.; Rheinheimer, M. I.; Wyer, S. B.; Bossard, G. E.; Higgins (III), J. D. *Inorg. Chem.* **1995**, *34*, 1015-1021). This process is illustrated in Figure 1 with the synthesis of *cis*-[$PtCl_2(NH_3)(L)$] and *c,t,c*-[$PtCl_2(OH)_2(NH_3)(L)$] as examples. From the readily available and commonly used $K_2[PtCl_4]$ starting material, the synthesis of *cis*-[$PtCl_2(NH_3)(L)$] involves four steps and the synthesis of *c,t,c*-[$PtCl_2Y_2(NH_3)(L)$] requires five steps. The synthesis of these complexes according to the process known in the art gives low overall yield. US Patent No. 4,329,299 discloses an overall yield from $K_2[PtCl_4]$of less than 8 %, while overall yields of 20-30 % have been reported in US Patent No. 5,665,771 and in the literature (Khokhar *et al.* and Giandomenico *et al.*). The low overall yield is due to the many stages involved in the process and to the difficult and low yielding conversion of $[PtCl_2(NH_3)_2]$ to $[PtCl_3(NH_3)]^-$, which requires the use of expensive Pt catalyst. The synthesis of $K[PtCl_3(NH_3)]$ from $[PtCl_2(NH_3)_2]$ is also not particularly robust and large scale synthesis producing $K[PtCl_3(NH_3)]$ of consistent quality is difficult to achieve. The process described above further requires the use of silver and iodide ions, and generates silver and iodide contaminated waste products.

US Patent 4,533,502 and UK Patent GB 2137198A disclose a synthetic process to prepare [$PtX_2(L)(L')$] where L and L' are ligands bonded through amine nitrogen and $L \neq L'$ (Rochon, F. D.; Kong, P.-C. *UK Patent GB2137198A* (**1984**) and Rochon, F. D.; Kong, P.-C. *US Patent 4533502* (**1985**)). The process is known in the art and the details of this synthetic process has been published (Courtot, P.; Rumin, R.; Peron, A.; Girault, J. P. J. *Organometallic Chem.* **1978**, *145*, 343-357 and Rochon, F. D.; Kong, P.-C. *Can. J. Chem.* **1986**, *64*, 1894-1896). Figure 2 illustrates the process with [$PtCl_2(L)(L')$] as an example. From $K_2[PtCl_4]$, the process disclosed in US Patent 4,533,502 and UK Patent GB 2137198A

involves 4 steps and the isolation of 3 intermediate products. The oligomer intermediate product is represented by $[PtLI_2]_x$ where x =2 to 4; multiple oligomer species are possible. The overall yield from $K_2[PtCl_4]$ was not disclosed in the patent. Silver and iodide ions are used in the process and corresponding silver and iodide contaminated wastes are generated.

$[PtCl_3L]^-$, where L is an amine other than NH_3, represent an intermediate in the present invention. The preparation of $[PtCl_3L]^-$ from a dilute solution of $K_2[PtCl_4]$ in dimethylformamide (DMF) where L are pyridine and pyridine derivatives has been reported (Rochon, F. D.; Kong, P.-C. *Can. J. Chem.* **1978**, *56*, 441-445 and Rochon, F. D.; Beauchamp, A. L.; Bensimon, C. *Can. J. Chem.* **1996**, *74*, 2121-2130). The preparation of $[PtCl_3L]^-$ in solvents other than DMF or H_2O, or with amine other than pyridine and pyridine derivatives have not been reported. The synthesis of $K[PtCl_3L]$ in DMF as reported in the literature was performed at 65-80 °C and the yields of the isolated product ranged from 40 % to 90 % depending on the pyridine derivative. Synthesis of $[PtCl_3L]^-$ in DMF can produce reactive or unstable Pt DMF complexes that could interfere with subsequent reactions or decompose to give insoluble black Pt impurities. For example in *Can. J. Chem.* **1978**, *56*, 441, Rochon *et al* reported the precipitation of insoluble black material when $K[PtCl_3(2,6\text{-dimethylpyridine})]$ was dissolved in aqueous solution. It was also reported that an oily paste that contained $[PtCl_2(DMF)(\text{pyridine derivative})]$ and other impurities was obtained during the isolation of $K[PtCl_3(4\text{-methylpyridine})]$ and $K[PtCl_3(\text{pyridine})]$. Examples of $[PtCl_2(DMF)L]$ complexes have been reported (Kong, P.-C.; Rochon, F. D.; *Can. J. Chem.* **1979**, *57*, 682-684; Rochon, F. D.; Kong, P.-C.; Melanson, R. *Can. J. Chem.* **1980**, *58*, 97-101; and Rochon, F. D.; Melanson, R.; Doyon, M.; Butler, I. S. *Inorg. Chem.* **1994**, *33*, 4485-4493).

Citation of the above documents is not intended as an admission that any of the foregoing is pertinent prior art. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents. Further, all documents referred to throughout this application are incorporated in their entirety by reference herein. Specifically, the present application claims benefit of priority to U.S. provisional patent application serial number 60/128,939, which was filed on April 13, 1999 and which provisional patent application is incorporated in its entirety by reference herein.

INTERNATIONAL SEARCH REPORT

Inte. onal Application No
PCT/CA 00/00385

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F15/00 //A61K31/28,A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 126, no. 14, 7 April 1997 (1997-04-07) Columbus, Ohio, US; abstract no. 194433, TALMAN, EDUARD G. ET AL: "Crystal and Molecular Structures of Asymmetric cis- and trans-Platinum(II/IV) Compounds and Their Reactions with DNA Fragments" XP002141047 abstract & INORG. CHEM. (1997), 36(5), 854-861 , --- -/--	1,67,68

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL ABSTRACTS, vol. 108, no. 24, 13 June 1988 (1988-06-13) Columbus, Ohio, US; abstract no. 215224, ROCHON, F. D. ET AL: "Synthesis and studies of platinum(II) compounds of the types K'Pt(amine)Cl3! and 'Pt(amine)(acetonitrile)Cl2!" XP002141048 abstract & INORG. CHIM. ACTA (1988), 143(1), 81-7 , ---	1,67,68
A	CHEMICAL ABSTRACTS, vol. 89, no. 4, 24 July 1978 (1978-07-24) Columbus, Ohio, US; abstract no. 35686, KONG, PI-CHANG ET AL: "Reactions of potassium tetrachloroplatinate(II) with pyridine derivatives in dimethylformamide and synthesis of potassium trichloro(pyridine)platinum(II)" XP002141049 abstract & CAN. J. CHEM. (1978), 56(4), 441-5 , cited in the application -----	1,67,68

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